REMARKS

Applicants respectfully request entry of the amendments hereinabove, reconsideration of the Office Action mailed on June 25, 2003 and allowance of the application.

Claims 1, 7-10, 21, 27, 44, 63-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of pulmonary hypertension with the PDE5 inhibitor of sildenafil, does not reasonably provide enablement for the prevention of pulmonary hypertension with the PDE5 inhibitor sildenafil. The rejection states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The rejection under 35 U.S.C. 112, first paragraph follows:

> The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art: (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.
>
> (1) The nature of the invention:
> The instant invention is directed to the prevention of pulmonary hypertension with the PDE5 inhibitor sildenafil. The method comprises administering the PDE5 inhibitor sildenafil for the prevention of pulmonary hypertension.
>
> (2) The state of the prior art:
> The compound of the invention is the PDE5 inhibitor sildenafil. However, the prior art reference of Ellis et al. of WO 94/28902 teach a variety of treatments for the compound sildenafil and its derivatives, but Ellis et al. do not teach of the prevention of pulmonary hypertension with sildenafil.
>
> (3) The relative skill of those in the art:
> The relative skill of those in the art of is high.
>
> (4) The predictability or unpredictability of the art:
> The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different

circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F. 2d, 833, 839, 166 USPQ 10, 24 (CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fischer, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 999 F.2d 1557, 1562, 29 USPQ2d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of the PDE5 inhibitor of sildenafil and its derivatives prior to filing of the instant invention was an unpredictable art.

(5) The breadth of the claims:

The instant claims are very broad. For instance, claim 1 is directed to the PDE5 inhibitors, namely sildenafil. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.), cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented:

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fischer, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 4;27 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of a PDE5 inhibitor sildenafil to be effective in preventing pulmonary hypertension is insufficient for enablement. The specification provides no guidance, in the way of enablement for the prevention of pulmonary hypertension with

PDE5 inhibitor of sildenafil other than the prevention of pulmonary hypertension with PDE5 inhibitor of sildenafil. In addition, the specification does not provide any enablement the prevention of pulmonary hypertension with PDE5 inhibitor of sildenafil. See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

(7) The presence or absence of working examples:

As stated above, the specification discloses the treatment of pulmonary hypertension with PDE5 inhibitor sildenafil. However, the instant specification only has enablement for the treatment of pulmonary hypertension with PDE5 inhibitor of sildenafil.

(8) The quantity of experimentation necessary:

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the how the PDE5 inhibitor sildenafil is used for the prevention of pulmonary hypertension when the instant specification only provides enablement for the treatment of pulmonary hypertension with the PDE5 inhibitor sildenafil.

Applicants traverse the rejection of the claims (as amended) under 35 U.S.C. 112, first paragraph.

Applicants submit that their claims are enabled, however, in the interests of expediting prosecution Applicants have herein amended the claims to delete the phrase "preventing" without waiver or prejudice against refilling.

Claims 1, 7, and 9 are rejected under 35 U.S.C. 12, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention. The rejection states that the valence number of two carbon atoms is exceeded at the two bridgeheads in compound of formula d). this ambiguity renders the claim vague and indefinite.

Applicants note the rejection of the claims under 35 U.S.C. 112, first paragraph and thank the Examiner for pointing out this clerical error. Since Applicants have deleted the claimed structure (see Remarks below) the 112 rejection is moot.

Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Takahasi et al., which has a publication date of 19961997 for the instantly claimed compound entitled d) of claim 1. The rejection states that Takahashi et al. describe administration of E4021, which is a type V phosphodiesterase inhibitor. The rejection also states that Takahashi et al. are directed to the administration of a type V phosphodiesterase inhibitor to protect against the development of right ventricular overload and medial thickening of pulmonary arteries in order to treat pulmonary hypertension.

Applicants traverse the rejection of claims 1 and 7 (as amended) under 35 U.S.C. 102 as being anticipated by Takahashi et al.

The Court of Appeals for the Federal Circuit, in ruling on the standard for anticipation under 35 U.S.C. §102(b), stated

> [i]t is elementary that an anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice or device.

In re Donohue, 226 U.S.P.Q. 619, 621 (1985); and "...exclusion of a claimed element from a prior art reference is enough to negate anticipation by that reference." Atlas Power Co. v. E. I. duPont DeNemours & Co., 224 U.S.P.Q. 409, 411 (1984).

Applicants submit that amended claim 1 (and accordingly, dependent claim 7) are not anticipated by Takahashi et al., since the species described in Takahashi et al., has been deleted from claim 1.

Claims 1, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al., which has a publication date of 19961997 for the instantly claimed compound entitled d) of claim 1. The rejection states that Takahashi et al. describe the administration of E4021, which is a type V phosphodiesterase inhibitor. The rejection also states that Takahashi et al. are directed to the administration of a type V phosphodiesterase inhibitor to protect against the development of right ventricular overload and medial thickening of pulmonary arteries in order to treat pulmonary hypertension. The rejection notes that the determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug.

Applicants traverse the rejection of claims 1, 7 and 9 under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al. Applicants submit that the claims are not obvious in light of Takahashi et al. Applicants submit that the art must be taken as a whole and that a review of the full publication of Takahashi et al. (included herewith) does not provide a sufficient basis for a prima facie case.

Applicants further submit that even assuming arguendo that the reference relied on by the Examiner makes Applicants' invention "obvious to try", "obvious to try" is not the proper standard for patentability. Further, the Examiner has not made out a *prima facie* case of obviousness because, *inter alia* (1) the references provide no effective motivation or suggestion that the claimed PDE V inhibitors could or should be tried in the treatment of pulmonary hypertension and (2) even allowing, *arguendo*, that any such suggestion or motivation were found in these references, the references provide no reasonable expectation of success.

The law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Applicants submit that the last sentence of the reference clearly summarizes the content of the reference "Our results suggest that the type V phosphodiesterase inhibitor, E4021, administered orally may prove efficacious in the management of patients with pulmonary hypertension and right ventricular overload" (underlining added for emphasis). Applicants submit that even assuming arguendo that there is a suggestion in the art to use Applicants' claimed compounds to treat pulmonary hypertension there is clearly not a reasonable expectation of success since the author admits that further work must be done and that there is only a suggestion that the type V PDE inhibitors may work. This is just an invitation to conduct further experimentation.

Claims 1, 7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kato et al. of JP 09059159 A2, which has an issue date of March 4, 1997 for the instantly claimed compound entitled d) of claim 1. The rejection states that Kato et al. teach a 2-(4-carboxypiperidino)-4-(3,4-methylenedioxybenzyl)amino-6-chloroquinazoline sodium salt. The rejection also states that Kato et al also teach that these compounds are useful for the treatment of pulmonary hypertension. The rejection also states that the determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug. The rejection reasons that it would have been obvious to one having ordinary skill in the art to employ the compound of Kato et al. even though Kato et al. is silent to the functional activity of PDE5 inhibitory activity of this compound. The rejection concludes that as a result, the instant invention is rendered obvious in view of Kato et al. since the determination of dosage and methods of using is well within the purview of the skilled artisan.

Applicants traverse the rejection of claims 1, 7 and 9 under 35 U.S.C. 103(a) as being unpatentable over Kato et al.

Applicants submit that the claims are not obvious in light of Kato et al. because the art must be taken as a whole and a review of the full publication of Kato et. al. (Applicants will supply a copy of a translation of the entire patent as soon as a translation is completed) does not provide a sufficient basis for a prima facie case. First, Applicants submit that claim 1 (as amended) is not anticipated by Kato et al. Accordingly, there is no teaching of Applicants' claimed compounds.

Applicants note the admission by the Examiner that Kato et al. is silent to the functional activity of PDE5 inhibitory activity of this compound. Accordingly, Applicants submit that there is no motivation in Kato et al. to modify the compound disclosed in Kato et al. to achieve Applicants' compounds since Kato does not relate the activity to PDE V activity. Since the PDE V enzyme target is not mentioned there is no way of determining what structural modifications would maintain the activity of Kato et al.'s compound.

Applicants submit that their claims are unobvious in light of the cited reference. Applicants further submit that even assuming arguendo that the reference relied on by the Examiner makes Applicants' invention "obvious to try", "obvious to try" is not the proper standard for patentability. Further, the Examiner has not made out a *prima facie*

case of obviousness because, *inter alia* (1) the reference provides no effective motivation or suggestion that the claimed PDE V inhibitors could or should be tried in the treatment of pulmonary hypertension and (2) even allowing, *arguendo*, that any such suggestion or motivation were found in these references, the references provide no reasonable expectation of success.

The law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Applicants submit that Kato et al. does not provide a reasonable expectation of success that Applicants' claimed compounds would be useful for the treatment of pulmonary hypertension since, for example, Kato et al. does not relate his compounds to PDE V inhibition, the compounds of Kato et. al. are distinct from Applicants' claimed compounds and there is no motivation in Kato et al. to modify his compound to achieve Applicants' compounds (or that if such modification were to occur it would result in active compounds).

Claims 1 and 7-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. of WO 94/28902 possessing a publication date of December 22, 1994, especially for sildenafil and its derivatives. The rejection states that Ellis et al. teach compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). The rejection also states that this selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). The rejection also states that the skilled artisan would have been motivated to treat patients with pulmonary hypertension irrespective of its cause, such as respiratory distress, neonatal hypoxia, post operatively, chronic hypoxia, COPD because Ellis et al. clearly disclose to the artisan that these inhibitors of cGMP PDE are used to

treat both hypertension and pulmonary hypertension. The rejection also states that Ellis et al. specifically teach inhibitors of cGMP PDEs with the compounds of formula (I). The rejection notes that Ellis et al. disclose of "[a] particularly preferred group of compounds of formula (I)" is obtained when R^1 is methyl; R^2 is n-propyl; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12}))-piperazinyl group; and R^{12} is methyl, (see page 6, 2nd full paragraph). The rejection also states that Ellis et al. also teach of pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs). The rejection states that Ellis et al. teach various modes of administration for these compounds, inter alia, oral and parenteral administration, (see page 10). The rejection states that Ellis et al. further teach of a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The rejection reasons that the determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug.

Applicants traverse the rejection of claims 1 and 7-112 under 35 U.S.C. 103(a) as being unpatentable over Ellis et al.

Applicants claims are for example, directed to the use of certain cGMP PDE **V** inhibitors (e.g., sildenafil) for the treatment of e.g., pulmonary hypertension (underlining and bold added for emphasis).

Applicants submit that their claims are unobvious in light of Ellis et al. Applicants further submit that even assuming arguendo that the reference relied on by the Examiner makes Applicants' invention "obvious to try", "obvious to try" is not the proper standard for patentability. Further, the Examiner has not made out a *prima facie* case of obviousness because, *inter alia* (1) the reference provides no effective motivation or suggestion that the claimed PDE V inhibitors could or should be tried in the treatment of pulmonary hypertension and (2) even allowing, *arguendo*, that any such suggestion or motivation were found in this reference, the reference provides no reasonable expectation of success.

The law is emphatic that "obvious to try" is NOT the test of obviousness under 35 U.S.C. §103. American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Applicants submit that Ellis et al. does not provide a reasonable expectation of success that Applicants' claimed compounds would be useful for the treatment of pulmonary hypertension since, for example, Ellis et al., does not relate the treatment of pulmonary hypertension to PDE V inhibition. Ellis et al. (merely through the EP0526004 reference) relates the treatment of pulmonary hypertension to generalized cGMP PDE inhibition.

Applicants claims are for example, directed to the use of certain cGMP PDE V inhibitors (e.g., sildenafil) for the treatment of e.g., pulmonary hypertension. Applicants submit that the art must be taken as a whole and both EP 0463756 and EP0526004 are relevant since they are described in the Ellis et al. passage that is referred to in the rejection and they are the basis for that Ellis et al. passage. In the pertinent passage in Ellis et al., EP 0463756 and EP0526004 there is description of the utility of cGMP PDE inhibitors but no mention of cGMP PDE **V** inhibitor utility (or that any cGMP PDE **V** activity of the recited compounds would be useful for the treatment of pulmonary hypertension). Thus, there is no suggestion that cGMP PDE V inhibitors would be useful for the treatment of pulmonary hypertension or that there is a reasonable likelihood of success for that utility (both being a requirement under current law). There are a number of isoforms of cGMP PDE and cGMP PDE V is only one possibility.

Further, neither EP 0463756 nor EP0526004 describe the use of Applicants' claimed compounds to treat pulmonary hypertension. Again, Applicants submit that the art must be taken as a whole and both EP 0463756 and EP0526004 are the basis for the Ellis et al. passage referred to in the rejection. While EP 0463756 describes that cGMP PDE inhibitors are useful for treating various disorders, EP 0463756 does not mention the use of any cGMP PDE inhibitors for the treatment of pulmonary hypertension. Applicants submit that the absence in EP 0463756 of the recitation of

pulmonary hypertension (in a lengthy list of other indications) as an indication for cGMP PDE inhibitors strongly implies that cGMP PDE inhibitors are not useful for the treatment of pulmonary hypertension (at a minimum it certainly does not provide a reasonable likelihood of success).

In addition, since sildenafil is included in EP 0463756 and since EP 0463756 implies that sildenafil is not useful for the treatment of pulmonary hypertension claims 21-112 directed to the use of sildenafil are not obvious in light of the art when taken as a whole.

Further, while EP0526004 does describe that certain cGMP PDE inhibitors are useful for treating pulmonary hypertension EP0526004 does not describe the use of any of Applicant's claimed compounds for any indication.

Accordingly, Applicants submit that when the art is taken as a whole (which it must be) a careful review of Ellis et al.'s statement regarding the utility of the cGMP PDE compounds, along with a review of the references (i.e., EP-A-0463756 and EP-A-0526004) that form a basis for Ellis's statement do not suggest or provide a reasonable likelihood of success that Applicants' claimed compounds would be useful in the treatment of pulmonary hypertension. In the pertinent passage Ellis et al. states "utilities already disclosed for the said compounds in EP-A-0463756 and EP-A-0526004 namely in the treatment of ...". Thus, Ellis et al. is referring to the utilities disclosed in EP-A-0463756 for the compounds of EP-A-0463756 and Ellis et al. is referring to the utilities disclosed in EP-A-0526004 for the compounds disclosed in EP-A-0526004. However, as is stated in the paragraph immediately above, EP 0463756 does not mention the use of any cGMP PDE inhibitors for the treatment of pulmonary hypertension and EP0526004 does not describe the use of any of Applicant's claimed compounds for any indication. While EP-A-0526004 does mention the use of certain cGMP PDE inhibitors for the treatment of pulmonary hypertension it does not suggest that Applicants' claimed compounds would be useful for the treatment of pulmonary hypertension or that there is a reasonable likelihood of success for such treatment. Again, EP 0463756 is silent as to pulmonary hypertension.

Claims 1, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. of WO 94/28902, which has a publication date of December 22, 1994, for the instantly claimed compounds entitled c) and e) and f) of claim 1. The rejection states that Ellis et al. teach compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). The rejection states that the

selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). The rejection states that Ellis et al. specifically teach inhibitors of cGMP PDEs with the compounds of formula (I). The rejection notes that Ellis et al. disclose of "{a} particularly preferred group of compounds of formula (I)" is obtained when R^1 is methyl; R^2 is n-proply; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; and R^{12} is methyl, (see page 6, 2nd full paragraph). The rejection states that the compounds disclosed by Ellis et al. have a structurally similar core structure with the 1,3-diaziny-4-keto moiety and other identical substituents on position no. 2 of the 1,3-diaznyl ring moiety. The rejection also states that the physiological activities are analogous. The rejection states that the claims differ from the prior art by having an imidazole moiety and an indole moiety, respectively instead of the pyrazole moiety of Ellis et al. The rejection also states that Ellis et al. teach pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs). Ellis et al. teach of various modes of administration for these compounds, inter alia, oral and parenteral administration, (see page 10). The rejection states that Ellis et al. further teach a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The rejection also states that the determination of a dosage having the optimium therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maxijum effect of the drug. The rejection reasons that one having ordinary skill in the art would have been motivated to select the claimed compound with the expectation that a substitution of a heterocyclic ring moiety, such as imidazole or indole moieties, for another, namely a pyrazole moiety, would not significantly alter the analogous properties of the compound of the reference due to the close structural similarity of the compounds. The rejection concludes that for these reasons the instantly claimed compounds entitled c) and e) and f) of claim 1 are rendered obvious over Ellis et al.

Applicants traverse the rejection of claims 1, 7 and 9 under 35 U.S.C. 103(a) as being unpatentable over Ellis et al.

Applicanats submit that claims 1, 7 and 9 are not obvious over Ellis et al. at least for the reasons described in the response above.

Based on the foregoing, favorable action on claims 1-10 and 21-112 is requested.

Authorization is hereby provided to charge any additional fees required, or to credit any overpayment to Deposit Account No. 16-1445. Two copies of this paper are enclosed.

Respectfully Submitted,

12/24/2003
Date

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